MEMORANDUM

DATE: May 9, 2001

FROM: Director
Division of Neuropharmacological Drug Products/HFD-120

TO: Members, Peripheral and Central Nervous Systems Drugs Advisory Committee

SUBJECT: Briefing Document for June 6, 2001 PCNS Advisory Committee Meeting to Discuss NDA 21-196, for the use of Xyrem (gamma hydroxy butyrate) in the treatment of cataplexy and daytime sleepiness in patients with narcolepsy

On 6/6/01, the PCNS Advisory Committee will meet to discuss NDA 21-196, submitted on 9/30/00 by Orphan Medical, Inc., for the use of Xyrem (gamma hydroxy butyrate, GHB) in the treatment of cataplexy and excessive daytime sleepiness in patients with narcolepsy. The application contains the results of 4 randomized controlled trials, as well as safety data. In addition, the sponsor has proposed an extensive Risk Management program, which is designed to 1) make both physicians and patients aware of some of the unique risks associated with Xyrem's use, 2) help minimize the risks to patients, and 3) help decrease the possibility that people other than those for whom it is prescribed will be exposed to the drug.

As you know, the meeting was originally to be held on March 15, 2001. However, prior to that date, the Agency's Division of Scientific Investigations issued its findings of a routine inspection of the records of Dr. Martin Scharf, an individual investigator who had treated about 140 patients under his own IND, and whose data (representing about 1000 patient-years of exposure, or about 70% of the total patient exposure in the NDA) had been submitted by the sponsor in support of the safety of GHB. This investigation raised serious questions about the reliability of the data in this study, primarily related to the inspectors' inability to locate critical source documents. Because Dr. Scharf's data constituted such a large proportion of the safety data base, and because the critical source documents necessary to confirm the sponsor's presentation of this data were not available, the Agency informed the sponsor that the NDA could not be approved without additional assurances that Dr. Scharf's data were valid.

As a result, the sponsor undertook a detailed and extensive review of Dr. Scharf's records, in an attempt to validate the presentation of this data in their NDA. This effort resulted in the submission of an amendment which contained a re-analysis of the data from Dr. Scharf's study. This amendment focused (though not exclusively) on the experience of the 80 patients in Dr. Scharf's study who did not go on to be treated under the sponsor's Treatment IND. Because the Agency did not have assurance that the ultimate disposition of these 80 patients was known, the amendment primarily focused on the current status of these patients, as well as serious adverse events that they may have suffered and the reasons for drug discontinuation.

The submission of the amendment resulted in an extension of the original due date for the application (the current due date is July 2, 2001), and the re-scheduling of the Committee meeting.

In addition to this memo, we are including several reviews of the relevant data as background for the meeting. We are including reviews of the safety and efficacy data performed by Dr. Ranjit Mani, medical officer in the division, as well as a review of the efficacy data performed by Dr. Sharon Yan, of the Division of Biometrics. In addition, we are including a memo from the Controlled Substances Staff, which will provide some background about the scheduling of this drug under the Controlled Substances Act, as well as some information about reports of abuse of illegal GHB.

Finally, we are including Dr. Mani's detailed review of the sponsor's amendment containing the re-analysis of the data generated by Dr. Scharf. This review also contains the sponsor's responses to several questions the review team asked related to issues raised by our review of the sponsor's own data (in particular, we asked for a more detailed review of neuropsychiatric adverse events, including confusion, as well as convulsions, and reported blood sugar and liver function abnormalities, and Dr. Mani has prepared a discussion of events reported as sleepwalking). While this review is, of course, well worth reading, we recognize that we are sending you a large number of documents (in addition to the documents prepared by the sponsor and being sent to you under separate cover). For this reason, Dr. Mani has prepared a brief summary of his conclusions about the re-submission of the Scharf data, which he has included as Section 20 of his primary Safety Review, and which captures the important issues.

Briefly, GHB is ubiquitous in human tissues, although its function is not well known. Since the early 1990's, there have been reports of extensive use of GHB for recreational purposes, (including by body builders as a substitute for steroids). Prior to 1990, it was available in health food stores, but it was subsequently removed when the Agency became aware of a number of reports of abuse resulting in serious outcomes, including death and respiratory arrest. Although it was difficult to absolutely implicate GHB in these cases (partly because these reports were often incomplete and poorly documented, people often had taken other drugs and alcohol, it was often unclear how much GHB a person had taken, or even if GHB had been taken, etc.), the Agency took GHB off health food store shelves as a public health measure (GHB is known to be a powerful CNS depressant, and many of these reports were of varying degrees of decreased level of consciousness and respiratory depression, which were consistent with the known pharmacology of GHB). Illicit use of GHB and related products has continued after the removal of GHB from stores.

Because of these reports and the known continued illicit use of this compound, Congress scheduled GHB as a Schedule I drug under the CSA in February, 2000, and considered its use under the IND as Schedule III. If Xyrem is approved, it will be as a Schedule III drug.

Based on the results of a single controlled trial which supported an effect of GHB in treating cataplexy in patients with narcolepsy, and the sponsor's commitment to provide the results of a second study, the Agency granted a Treatment IND to the sponsor in December, 1998.

In this memo, I will briefly review the evidence for the effectiveness of GHB for the sponsor's proposed claims, as well as the safety data presented in the NDA. I will also briefly describe the major aspects of the sponsor's Risk management plan, and raise some of the questions we would like you to consider during your discussions and deliberations at the 3/15/01 meeting.

EFFECTIVENESS

As noted above, the sponsor has submitted the results of 4 controlled trials. Two of these trials were sponsored and performed by the sponsor (Studies GHB-2 and GHB-21). Two others (Lammers, Scrima) were performed by independent investigators, and the sponsor has obtained the data from these studies.

STUDY OMC-GHB-2

This was a randomized, double-blind, parallel group, multi-center trial in which patients were randomized to one of four treatment groups: Placebo, 3gm/day, 6gm/day, or 9gm/day. The drug was dissolved in water, and was given twice/day, at bedtime and 2.5-4 hours later.

The study consisted of 5 phases:

1) **Screening Period**-lasted 1 day-4 weeks, in which patients were withdrawn from tricyclics and other treatments for cataplexy
2) **Washout Period**-lasted 5-28 days, in which the pharmacological effects of previous treatments were expected to resolve, the patient stabilized, and in which patients were trained in the use of a diary to record the study data on a daily basis
3) **Baseline Period**-lasted 2-3 weeks, during which the patients were observed and required to have a stable frequency of cataplexy attacks
4) **Treatment Period**-lasted 4 weeks

5) **Follow-Up Period**-lasted 3-5 days

Patients with a diagnosis of narcolepsy for at least 6 months, with a history of excessive daytime sleepiness and at least 3 cataplexy attacks/week for the last 2 weeks of the baseline period were eligible for enrollment into the treatment period.

Patient visits were scheduled once during the first 3 periods and the Follow-Up Period, and at the beginning of the Treatment Period and at 14 and 28 days of the Treatment Period. Patients were to be contacted at least 3 times/week during all phases.

The primary outcome measure was the Change from Baseline in the Number of Cataplexy Attacks/Week, utilizing data from the last 2 weeks of baseline and the last 2 weeks of treatment. This outcome was to be analyzed with an ANOVA if the data were normally distributed, and by a Kruskal-Wallis test if not. The ANOVA was to be based on a model containing terms for treatment group, site, and treatment by site interaction, if the interaction was found to be statistically significant.

The primary analysis was to performed on the grouped data (i.e., drug vs placebo). If this was significant at a two-tailed alpha of 5%, pairwise comparisons were to be made for the individual doses.

An ANCOVA was also to be performed with the baseline cataplexy rate as the covariate. No prospective document submitted (protocol or amendments) contains any details of this analysis. However, in the study report, the sponsor states that a prospective plan was written for performing a log transformation of the data if not normally distributed for the purposes of this ANCOVA.

Secondary outcomes were:

1) Complete cataplexy attacks
2) Partial cataplexy attacks
3) Daytime sleepiness measured on the Epworth Sleepiness Scale
4) Clinical Global Impression of Severity, a rating performed by the physician in which the patient was compared to the population of patients with narcolepsy
5) Clinical Global Impression of Change
6) Number and duration of awakenings at night
7) Total amount of sleep each night
8) Number and duration of inadvertent naps an sleep attacks
9) Number and occurrences of hypnagogic hallucinations or sleep paralysis
10) Quality of sleep, level of alertness, and overall ability to concentrate measured on a 4 point scale (1=excellent, 4=poor).

RESULTS

A total of 136 patients were randomized to treatment at 16 centers. The following chart displays patient disposition throughout the trial (taken from Dr. Mani's review, page 13):

	Placebo	3 Gm	6 Gm	9 Gm
Randomized	34	34	33	35
Completed	33	30	29	28

Most of the discontinuations at the 9 gm dose were related to adverse events (6/7).

Essentially all patients had cataplectic attacks and excessive daytime sleepiness during the 3 months prior to study, by history, with from 94-97% of patients having sleep attacks as well. The incidences of sleep paralysis and hypnagogic hallucinations were considerably lower, about 70-80%.

The following results for the primary variable are presented below:

Mean (Median) Change From Baseline in Number of Cataplexy Attacks/Week

	Baseline	Endpoint	Change	P-value
Placebo (N=33)	35.1 (20.5)	24.0 (16.3)	-11.1 (-4.3)	
3 GMS (N=33)	28.6 (20.0)	19.5 (9.5)	-9.1 (-7.0)	0.52
6 GMS (N=31)	33.8 (23.0)	24.6 (8.0)	-9.2 (-9.9)	0.053
9 GMS (N=33)	35.7 (23.5)	14.4 (8.7)	-21.3 (-16.1)	0.0008

The overall test yielded a p-value of 0.002.

These results, presented by the sponsor, are derived from an ANCOVA utilizing log transformed data. As noted earlier, the sponsor asserts (without documentation) that such a transformation was prospectively planned. However, even if such an analysis was planned, it was not planned as primary. Dr. Yan has performed the Kruskal-Wallis test called for in the protocol in the case of non-normally distributed data. The overall test was significant (p=0.01), with the following p-values obtained for the pair-wise comparisons:

3 gms vs placebo	0.47
6 gms vs placebo	0.15
9 gms vs placebo	0.003

An ANOVA on log transformed data (analogous to the analysis described in the protocol if the data had been normally distributed) was also performed by Dr. Yan. Although the results were not reported in her review, she informs me that there was a statistically significant overall result, with the 9 gm/day dose showing the greatest effect.

Secondary Outcomes

Dr. Mani describes in detail the results of analyses of the secondary measures. In general, where overall nominal statistical significance is obtained (on all secondary measures except number of hypnagogic hallucinations, number of episodes of sleep paralysis, total amount of nighttime sleep, and number of total cataplexy attacks), the largest and consistently significant effects are seen with the 9 gm dose group; some of the measures are also significant for the 6 gm group. In particular, the results on the Epworth Sleepiness Scale are as follows:

	Change From baseline	P-value vs Placebo
Placebo	-2.0	
GHB 3 GM	-1.0	0.11
GHB 6 GM	-3.5	0.19
GHB 9 GM	-5.0	0.0001

The overall p-value (ANOVA) was 0.0006.

Nominal statistical significance is also noted for the overall test and the 9 GM group for the collapsed Clinical Global Impression of Change, in which patients in the original categories “much improved” and “very much improved” were classified as responders and all others were considered non-responders.

LAMMERS STUDY

This was a double-blind, placebo controlled, randomized, counter-balanced cross-over, single center study. Patients were required to have had sleep attacks during the day and at least 1 REM dissociation phenomenon (cataplexy, sleep paralysis, hypnagogic hallucinations). The study consisted of 3 phases:

1) Baseline Period-lasted 1 week
2) Treatment Period-2, 4 week periods
3) Washout Period-lasted 4 weeks

The last week of the Washout Period served as the Baseline for the second Treatment Period.

Patients were permitted to continue receiving any of their concomitant medications without dosage adjustment. The dose of GHB was 30 mg/kg, once at bedtime and again 4 hours later.

As Dr. Mani notes in his review (pages 30-31), a single primary outcome was not stated explicitly in the protocol. However, it did state that the study would be considered “positive” if improvement were to be shown on the following:

1) Number of cataplexy attacks/week
2) Global Therapeutic Impression of the patient, scored at both the end of the entire study as well as at the end of each treatment period (the latter was to be written in the daily diary)
3) Global Clinical Impression of the physician

No details of the structure of these global ratings were given in the protocol.

The protocol called for collection of the following additional data and outcomes which were, “…of secondary importance and will only be analyzed if effect is found in the primary variables”:

1) Number of sleep attacks
2) Visual analogue scale for daytime sleepiness
3) Multiple Sleep Latency Test improvement
4) EEG assessed stability of alertness during the day
5) Duration of slow wave sleep
6) Decrease in number of phase shifts at night
7) Change in mood

The section of the protocol describing the analysis of the trial was extremely brief, but did state explicitly that the difference between placebo and drug would be tested with the Wilcoxon signed rank test, using the traditional 2 sided alpha of 5% as a measure of significance.

RESULTS

A total of 25 patients were enrolled into the following sequences:

Drug-Placebo	13
Placebo-Drug	12

One patient had no diary data for the first period and was excluded from the analysis. A second patient was determined to not have narcolepsy, but was included in the study report (though not in the analysis in the published paper).

The mean dose in this study was 4.75 Gms/night.

The results of the protocol specified analysis, as presented in the published article, are presented first. However, as Dr. Yan notes, she (and Dr. Jin and the sponsor) concludes that this is an inappropriate analysis in this setting, because the Wilcoxon test can not examine any possible period effect.

Protocol Specified analysis:

Mean Change From Baseline in Number of Weekly Cataplexy Attacks

	Baseline	Endpoint	Change	P-value
Placebo (N=23)	1.56	1.24	-0.32	
GHB (N=23)	1.26	0.56	-0.70	0.42

The sponsor performed an ANCOVA with log transformed data, ostensibly because such an analysis was performed for the first study, although they acknowledge that the transformed data also were not normally distributed. In addition, they justify this analysis because of the “wide variation” in the baseline frequency, and, as noted above, they believe that the protocol specified analysis (the Wilcoxon signed rank test) is inappropriate for a cross-over study. As Dr. Mani points out, the ANCOVA was done many years after publication and original analysis of the study.

Sponsor’s analysis:

Median Change From Baseline in Number of Weekly Cataplexy Attacks

	Baseline	Endpoint	Change	P-value
Placebo (N=24)	5.53	3.01	-2.52	
GHB (N=24)	3.99	1.47	-2.52	0.002

Dr. Yan, in her Table 13 (page 20 of her review) displays the results by sequence and period. These results are abstracted here:

	GHB/Pbo			**Pbo/GHB**		
	Baseline	Endpoint	Diff	Baseline	Endpoint	Diff
Period 1	1.35	0.56	-0.79	1.17	0.75	-.42
Period 2	1.17	1.19	0.02	0.78	0.45	-.33

There has been considerable discussion by the statisticians about the propriety of performing an ANCOVA on a cross-over trial with standard SAS PROC GLM software. At the request of Drs. Jin and Yan of the Division of Biometrics, the sponsor performed an ANCOVA utilizing a method described in an article by Patel (Patel, H.I., 1983. Use of Baseline Measurements in Two-Period Crossover Design in Clinical Trials. Commun. Statist.-Thero. Meth., 112(23), 2693-2712), and obtained a p-value of 0.037. Utilizing PROC MIXED in SAS yielded a p-value of 0.032. Dr. Jin independently performed the ANCOVA using the sponsor's program, and obtained the same result as the sponsor.

In order to assess the appropriateness of performing an ANCOVA on this data (as opposed to the appropriateness of the particular software used to run the analysis, the point addressed above), Dr. Yan stratified the change in cataplexy attacks by baseline frequency, using the median of the baseline frequency. This exploration supports the view that the results are dependent on the baseline frequency of cataplexy attacks. On the basis of this data, she concludes that an ANCOVA, with the baseline cataplexy rate as the covariate, is reasonable.

However, she also performed the standard ANOVA used for these designs, and obtained a p-value of 0.18, with a marginal mean difference between treatments in the number of cataplexy attacks of -.359 in favor of GHB (an ANOVA on log transformed data yielded a p-value of 0.12). The estimate of the between treatment difference obtained in the ANCOVA as originally performed by the sponsor (I do not have this estimate for the analysis using the Patel method) was -.480 in favor of GHB.

Finally, Dr. Yan also performed an ANCOVA of the first period data as a parallel group study. The estimate of the between treatment difference was -.258 in favor of GHB, but this difference was not statistically significant (p=0.15). This analysis was performed by Dr. Yan partly because there was some evidence of a carry-over effect, and the ANCOVA assumes no such effect (as she notes, this study was not adequately powered to reasonably detect such an effect).

Global Ratings

The sponsor did not report the results of the physician rated Global, saying that it was not recorded properly, apparently since the investigator, "…only reproduced the opinion of the patient…". Although not described in the protocol, the remaining patient rated Globals were described in the article as being a 4 point scale, with the following points:

0-No effect at all
1-Possibly beneficial
2-Beneficial
3-Strongly beneficial

Based on subsequent discussions with, and submissions by, the sponsor, the meaning of scale point 1 (possibly beneficial) remains unclear. Quoting from a submission dated 11/29/98, which was written after a discussion held with Dr. Lammers intended to clarify this point:

> He described the scale as one for which the patient felt some effect, but was not entirely sure that the effect was from the medication. The patient would also not be entirely sure that there was no effect from the medication.

In any event, the results were presented as dichotomous; that is, patients were classified as having had a “beneficial effect” (scale steps 2 and 3), or as having “no beneficial effect” (scale scores 0 and 1). The following results were obtained, first for the global rated at the end of the study, and next for the global rated at the end of each period:

		GHB Period	
		No effect	Beneficial
Placebo Period	No effect	8	15
	Beneficial	1	1

The p-value, by McNemar’s test, was 0.001.

		GHB Period	
		No effect	Beneficial
Placebo Period	No effect	11	10
	Beneficial	2	2

The p-value, by McNemar’s test, was 0.021.

Dr. Yan performed analyses on the uncollapsed data and first period data only, with p-values ranging from 0.003 to 0.010.

Secondary Measures

A number of secondary measures were assessed. Some of those reported were not included in the protocol. As Dr. Mani describes (page 37), Daytime Sleep Attacks, Severity of Daytime Sleepiness, and Nocturnal Awakenings were nominally significant. Only the Severity of Sleepiness was analyzed using the protocol specified Wilcoxon test; the other 2 were analyzed with an ANCOVA.

SCRIMA STUDY

This was a randomized, double-blind, placebo controlled counter-balanced cross-over trial in 20 patients. Patients were required to have a history of excessive daytime sleepiness, at least 10 cataplexy attacks during the 2 weeks of baseline, and at least 2 REM onsets and a sleep index of at least 75 on the Multiple Sleep Latency Test. The trial had the following design:

1) Baseline-14 days
2) Treatment Period-2, 29 day periods
3) Washout-6 days, between Treatment Periods 1 and 2, and after Period 2

Apparently, patients were withdrawn from their anti-cataplexy drugs during the Baseline Period. The total daily dose in this study was 50 mg/kg.

There were 2 primary outcome measures prospectively described in the protocol: 1) the number of cataplexy attacks/week, and 2) daytime sleepiness, as measured by the Multiple Sleep Latency Test (MSLT). The protocol **suggests** that the first outcome was to be assessed by comparing treatments on the difference between the mean number of cataplexy attacks during the fourth and first weeks of treatment, although it is not clear on this point. The analysis presented by the sponsor compared the treatments on the change from baseline in the mean number of cataplexy attacks for the entire 4 week treatment period. The MSLT was to be analyzed by comparing the results on Day 1 of each treatment period with those on Day 29.

A number of secondary measures were performed, including the number of arousals during sleep, number of sleep attacks, total sleep time, patient estimates of sleep latency, Stanford Sleepiness Scale ratings, number of naps, and number of naps/day.

The following results were obtained by the sponsor:

Mean Number of Cataplexy Attacks/Day

	Baseline	Week 1	Week 2	Week 3	Week 4	P-value (overall)
GHB	2.9	1.4	1.4	0.9	0.9	0.013
Placebo	2.9	1.5	2.0	2.1	1.9	

MSLT	0.085

Dr. Yan performed a repeated measures ANOVA of the difference in mean number of cataplexy attacks/week between Week 4 and Week 1 (as prospectively described in the protocol). She obtained a p-value for the between-treatment contrast of 0.037 (see her review, page 27). Her analysis of the MSLT yielded a p-value for the between-treatment contrast of 0.069.

STUDY 21

This was a randomized, placebo controlled trial performed at 14 centers designed to evaluate the long-term efficacy of GHB. Patients who had been receiving GHB for between 6 months and 3.5 years under one of several open-label protocols were randomized to receive their current dose of GHB (3-9 Gms; as noted by Dr. Mani, 80% of patients were taking a dose of between 6 and 9 Gms/day) or placebo for 2 weeks. The primary outcome was the change from baseline (the last 2 weeks on open-label GHB) in the frequency of cataplexy attacks/week.

The following efficacy results are taken from Dr. Mani's review:

	GHB (N=26)		Pbo (N=29)		P-value
	Baseline	Endpoint	Baseline	Endpoint	
Mean	9.0	12.6	15.7	50.4	<0.001
Median	1.9	1.1	4.0	21.0	

SAFETY

The sponsor has presented the safety experience for 504 unique patients with narcolepsy and 125 normal volunteers (the latter represent single dose exposure in pharmacokinetic studies). The experience has been presented by the sponsor in several cohorts: the clinical trial experience (the sponsor-run trials, including open label extensions and the Treatment IND experience, as well as the data from the Scrima study, N=402), the Lammers data (N=25), the Scharf data (N=143), and the Pharmacokinetic data (N=144; 19 patients and the 125 volunteers described above). Some patients were in several of these cohorts; for example, about 60 patients originally treated by Dr. Scharf were subsequently included in the sponsor's Treatment IND. The total safety data reflects about 1400 patient-years, with Dr. Scharf's experience comprising about 1000 patient-years (Dr. Scharf's IND has been in existence for over 16 years).

Overall, about 350 patients have received treatment for at least 6 months, with about 180 receiving treatment for at least 1 year. The vast majority of the long-term safety experience derives from Dr. Scharf's study.

As noted previously, serious questions had been raised about the reliability of Dr. Scharf's data as presented by the sponsor, based on our inability to reconstruct individual patient experiences from Dr. Scharf's original records. While the sponsor has made an effort to support its presentation of Dr. Scharf's data based on its own re-review of Dr. Scharf's records, there are still a number of important unanswered questions about the completeness and reliability of this data. While the brief summary of the safety data given below includes the Scharf data, the deficiencies in this sub-set of the sponsor's safety database need to be kept in mind.

Deaths

There were a total of 12 deaths in this experience; 1 in the Treatment IND, 11 in Dr. Sharf's study. The patient in the Treatment IND was a 47 year old woman with a history of bipolar disorder and head trauma who had received 6 Gms/day of GHB for about 1 year when she committed suicide by taking multiple drugs.

The deaths in Dr. Scharf's study occurred in patients who had been taking drug for between 1.2-10.4 years, and there seemed to be no clear relationship to drug in any of these cases. The sponsor states that only 5 of these deaths occurred within 30 days of the last dose of drug.

Serious Adverse Events

There were 3 serious adverse events in the controlled trials (ovariectomy, somniloquy, and mildly elevated LFTs) on drug, and none on placebo.

There were a total of 18 serious ADRs in the Clinical Trial database, which included 1 case of unresponsiveness and respiratory failure (a 64 year old man receiving 9 Gms/day for about 170 days; drug was permanently discontinued). Other serious ADRs included mental status changes (3 cases of acute confusional state; all resolved with drug discontinuation; 1 case of auditory hallucinations in a patient with a history of hallucinations, the event resolved with lowering of the dose).

There were a total of 54 patients who reported serious adverse events in Dr. Scharf's study. The greatest number (11, or 7.7%) were reported as "unevaluated reaction". Other less frequent serious ADRs are described in Dr. Mani's review.

Discontinuations

A total of 11 patients (10 on GHB, 1 on placebo) discontinued treatment due to an adverse event in the Controlled Trials cohort (all in Study GHB-2). A total of 7 were in the 9 Gm/day group, with one in the 3 and two in the 6 Gm/day groups. Events that led to discontinuation in the GHB group included acute confusion, increased sleepiness or sedation, weakness, nausea, one case of loss of bowel control while asleep. The placebo patient had insomnia.

In the entire Controlled Trials database, a total of 53 patients discontinued treatment due to an adverse event. Some of these events included sedation, suicide and suicide attempt, weakness, restless legs, sleepwalking, dizziness. Most of these events were rated as Mild or Moderate.

In the Scharf trial, 13 patients withdrew due to an adverse event (not including the 5 who died within 30 days of the last dose of drug). These events included 2 patients with presumed seizures (the reports are not particularly detailed), after 6 months and 1.8 years on drug. Dr. Mani, in his review of the amendment, describes some of the outstanding deficiencies in the documentation of these events (section 6.5.3, pages 17-18).

Other Adverse Events

The following table displays the incidence of some of the more frequent adverse events in the Controlled Trials database:

Event	GHB (N=147)	Placebo (N=79)
Dizziness	23%	3%
Headache	20%	15%
Nausea	16%	5%
Pain	12%	4%
Somnolence	12%	9%
Sleep disorder	9%	3%
Confusion	7%	1%
Vomiting	6%	1%
Incontinence, urine	5%	0%

Study 2 provided the only opportunity to assess any dose response for adverse events. The following events were dose related in this trial in descending order of frequency (the incidence presented is for the 9 Gm/day dose group): nausea, dizziness (34%), confusion, sleep disorder, somnolence, urinary incontinence (14%), sweating (11%), amnesia, anxiety, thinking abnormal, dysmenorrhea (6%), In the long-term, open data, there was an 8% incidence of urinary incontinence.

Many adverse events were noted in Dr. Scharf's experience, but this consisted of long-term, open, uncontrolled use, so it is difficult to interpret this data. Again, of interest, 23% of patients in this cohort were recorded as having had an adverse event listed as "reaction unevaluable". As Dr. Mani notes in his review of the amendment (Section 8, pages 27-29), it appears that none of these events are clearly related to GHB. A total of 23% of patients in Dr. Scharf's experience reported at least one episode of urinary incontinence.

Urinary Incontinence/Seizures

As noted above, there have been frequent reports of urinary incontinence in patients being treated with GHB, both in controlled trials and in open, uncontrolled exposure. In addition, 2 patients in the database experienced fecal incontinence.

Because GHB is known to cause seizures in animal models, the episodes of incontinence (as well as the relatively rare reports of seizures themselves) raised the possibility that GHB was causing seizures. The sponsor performed additional analyses to further define the relationship, if any, of the incontinence to possible seizure activity. This analysis included examining the relationship of other CNS adverse events to episodes of incontinence, consultation with experts, reviewing the medical literature, and performing EEGs in 6 patients who had experienced incontinence while being treated with GHB in the past. Of these 6, 4 had adequate EEG examinations (2 had polysomnographic EEGs examined retrospectively). One of the 6 had an episode of incontinence during the EEG recording; apparently, no seizure activity was noted on the EEG.

Many, if not most, of the episodes have occurred while the patient was sleeping. According to Dr. Scharf, none of the bed partners of his patients who experienced incontinence noticed or reported any seizure activity.

The sponsor has concluded that there is no affirmative evidence of an association of urinary incontinence and seizures in patients treated with GHB.

As Dr. Mani notes, however, the reports of convulsions in this database include few details. Again, as he notes, 1.4% of GHB treated patients in the controlled trials (N=2) had an event called "convulsion", compared to none in the placebo treated patients. In the Controlled Trials safety database, 2.5% of patients had such an event, and in Dr. Scharf's study, 6.3% of patients also had an event coded as "convulsion". At this time, the relationship, if any, between urinary incontinence and seizures in GHB treated patients, or between GHB use and seizures, in the absence of reported urinary incontinence, is unclear. Dr. Mani concludes (review of the amendment, Section 9.7, pages 34-5) that for almost all cases, there is little affirmative evidence that the episodes of incontinence reported occurred in the setting of a true seizure, although there was one case in which incontinence clearly, and one case in which it likely, occurred during a seizure. These 2 cases are also the only cases that are clearly seizures (with or without incontinence) that could reasonably be considered to have possibly been related to treatment with GHB, although, as Dr. Mani points out, in both cases there were other factors that could have been responsible for the seizures.

Neuropsychiatric Adverse Events

A total of 29% (41/143) of Dr. Scharf's patients were reported to have experienced at least one event in this category (including overdose, suicide attempt, depersonalization, depression, emotional lability, hallucinations, hostility, neurosis, paranoid reaction, stupor, thinking abnormal). Most of these (22/41) events were listed as depression. Four events were considered serious, and 2 resulted in drug discontinuation, although, as Dr. Mani suggests (review of the amendment, Section 11.8, page 49) it is difficult to affirmatively attribute these events to GHB in most cases.

In the Integrated Clinical Trials Database (N=402), a total of 12% (50/402) had at least one report of such an adverse event, again with depression being most common (27/50). In the controlled trial (GHB-2), there was no important difference in the incidence of these ADRs among any of the dose groups (placebo, 3, 6, or 9 gms of GHB).

Again, it is difficult to attribute these events to GHB use in most of the cases.

Confusion

A total of 7.5% (30/402) patients in the Integrated Clinical Trials database had at least one episode coded as confusion, with 0.5% (N=2) considered serious and 0.7% (N=3) responsible for drug discontinuation. In the controlled trial, 17% of the 9 gm/day dose group (N=6) experienced such an event, compared to 3% (N=1) in the placebo group, 9% (N=3) in the 3 gm/day group, and 3% (N=1) in the 6 gm/day group.

In Dr. Scharf's data, 7% (10/143) of patients had such an event reported, 1 of which was reported as serious.

It appears that GHB use can be associated with episodes of confusion.

Sleepwalking

A total of 2 patients in the controlled trial were reported to have had at least one episode of sleepwalking, both in the 9 gm/day group. It is not clear how many such patients there were in the Integrated Clinical Trials database, although 11% were reported to have had "sleep disorder" listed as an ADR (the sponsor did not further characterize this category of events).

In the Scharf study, a total of 35% (45/143) of patients were reported to have had at least one episode of sleepwalking, 4 of which were considered serious or potentially serious (one patient reportedly attempted to drink nail polish remover, one patient reportedly ingested an overdose of GHB while sleepwalking on 2 occasions, one of which resulted in coma, one patient was reportedly found in bed with a lighted cigar).

As Dr. Mani notes, given the relatively high frequency with which this adverse event has been reported (especially in the Scharf study) further characterization of sleepwalking as an adverse event is warranted.

Lab Tests

There were no systematic important changes in routine laboratory tests or EKG parameters.

Risk Management Program

Because GHB continues to be used illicitly as a recreational drug, and because it has powerful CNS sedative properties, the sponsor has proposed an extensive Risk Management Program to inform patients and physicians about the risks, to minimize the risks to the patients, and also, critically, to minimize the likelihood that people other than the patient for whom it is prescribed will be exposed to the drug. This latter point refers not only to diversion of the product for illicit purposes, but also to accidental ingestion by family members. (Xyrem is supplied as a liquid in 240 mL bottles containing 90 Gms of GHB. Patients are instructed to withdraw the appropriate amount of drug and place it in 2 dosing cups. The first dose is taken at bedtime, and the second dose is taken 2.5-4 hours later (the patient must wake up to take the second nightly dose). The second dose must be placed near the patient's bed, so that he or she does not have to get out of bed to take this dose. While these dosing cups have child-proof lids, there is concern that the drug could accidentally be ingested by a young child who sees a cup of liquid near their parent's bed. Further, the availability of a significant amount of the drug in a bottle [or several bottles] raises the concern that this could be relatively easily diverted.)

Dr. Mani has described the sponsor's proposal in detail. Briefly, GHB will be obtainable only through a centralized pharmacy. A physician will submit a prescription for the drug to this pharmacy, which will send out to the physician a number of educational materials which will familiarize the physician with the drug, its adverse effects, etc. At the same time, the pharmacy will ship the drug to the patient, also accompanied by educational materials. The patient must receive the shipment personally, or it will be returned to the pharmacy (in the rare case that the patient's insurance requires that the patient receive the drug from their local pharmacy, provisions for having the central pharmacy ship drug to the local pharmacy will be available). The patient will be required to return certain forms to the central pharmacy before subsequent shipments will be sent. All patients and prescribing physicians will be entered into a registry maintained by the centralized pharmacy. Close surveillance will be maintained for unusual events (e.g., a patient who requests refills at time points earlier than his or her scheduled refills, etc.).

DISCUSSION

The sponsor has submitted the results of 4 controlled trials that they believe establish the effectiveness of GHB as a treatment for cataplexy and excessive daytime sleepiness in patients with narcolepsy. Further, they have submitted safety data that they believe establish the safety of GHB when given at the effective doses and in conjunction with their proposed Risk Management program.

We will be asking the Committee to formally vote on the following questions:

1) Has the sponsor presented substantial evidence of effectiveness for their proposed claims for GHB as a treatment for cataplexy and excessive daytime sleepiness in patients with narcolepsy? If not, is there any reasonable claim for which the sponsor has presented substantial evidence of effectiveness?
2) Has the sponsor submitted sufficient data to establish the safety of GHB when used in accordance with their proposed Risk Management Program?

(It should be pointed out that as of this writing, the Agency has not re-inspected Dr. Scharf's records, although such a re-inspection is planned for the near future. In any case, there are still serious questions about the validity of the data from Dr. Scharf's site. Although we believe that there have been no adverse events reported from Dr. Scharf's data that would pose an absolute bar to approval – although some events need further characterization-the division is seriously considering requiring the sponsor to accumulate additional well-documented safety data to increase the number of patients in the NDA with reliable safety experience.)

Although we will not ask for a formal vote on other questions, we are very interested to hear your views on various aspects of the sponsor's submission, in particular the Risk Management Program.

Questions have been raised about the adequacy of this proposed program. In particular, some proposed additions to the proposed plan include:

1) requiring physicians to document that they have read the materials sent to them before the pharmacy fills the initial prescription
2) requiring patients to sign an informed consent form before receiving the initial shipment of drug

3) requiring patients to return registry forms before receiving the first shipment of drug
4) required post-marketing reporting of cases of abuse, dependence, diversion, and accidental overdose
5) using the pharmacy-maintained registry to prospectively and systematically gather adverse event data
6) requiring additional safeguards in patients' homes (e.g., keeping drug in a locked storage space)
7) additional warnings on the labeling of the dosage cups and/or bottle of GHB
8) requiring physicians to demonstrate safe use and appropriate dosage preparation to patients before the first prescription, and documenting that this has been accomplished
9) restricting prescribing of the product to, (or requiring initial diagnosis to be made by), physicians with specialized training in sleep disorders
10) restricting prescribing to only those patients with cataplexy (essentially eliminating off-label use)

The division has not yet taken a position on any of these proposals (some would be relatively easy to require, others might be quite difficult), and we are interested in your views on these questions, as well as, of course, on any other relevant issue.

I look forward to seeing you all in June, and thank you for your efforts in preparing for the meeting, and in advance for your efforts at the meeting.

Russell Katz, M.D.